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Prague, March 24, 2005

International Bureau of WIPO,
34 chemin des Colombettes
1211 Geneva 20
Switzerland

Re: **International Application PCT/CZ2004/000068**
(Applicant´s comments on the written opinion of the International Searching Authority)

Your ref.: PCT/CZ2004/000068
Our ref.: 150385/KB

This is to the written opinion of International Searching Authority (further only as "ISA") concerning the above-identified International Application (further only as "present application").

Item 2a) Inasmuch the ISA has no objections against the novelty of the process claims 2,3 of the present application we leave this issue without any comments.

Item 2b) As far as the novelty of the product claim 1 of the present application is concerned, the ISA deems that "*document D1 (WO 03/004505 A) discloses oxaliplatin: In the absence of proof to the contrary, it is assumed that the oxaliplatin of D1 falls within the scope of claim 1. Consequently, the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT*".

Our position to the above presented ISA´a reasoning is the following: If an product to protect is not the product itself but a system composed of the product together with

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all its accompanying impurities coming into consideration in the given case then such a system should be defined in the corresponding patent document (i.e. either in claims or at least somewhere in the description) not only by qualitatively specifying the product on its own but also both qualitatively and quantitatively specifying all the accompanying impurities, which means that the whole concerned system should be unambiguously defined. As both the processes to compare, i.e. process of D1 and that of the present application, proceed under the substantially same reaction schedule the accompanying impurities of the both processes are justifiably supposed to be qualitatively identical. These impurities are: oxalic acid, the alkali metals, silver and nitrates. Whereas the requirement to unambiguously define the whole system oxaliplatin/impurities is met for the present application (the proportions of the alkali metals, silver and nitrates are quoted in claim 1 while the proportion of oxalic acid is set up in example) this is not fulfilled at all in the case of D1 that is absolutely silent on proportions of the alkali metals, silver and nitrates which, in turn, means the system oxaliplatin/impurities of D1 is not fully defined. Under this state of facts, the question is how the ISA can be sure that the system of D1 is identical with that of the present application when having no knowledge of the quantity of the alkali metals, silver and nitrates present in system oxaliplatin/impurities of D1. To our mind, the system oxaliplatin/impurities of D1 has indeed no capacity to be used as an objection proving the non-novelty of the content of claim 1 of the present application in view of that there is an uncertainty regarding the whole composition of the system of D1. The thing is, if the way of objecting as presently used by the ISA was also taken for correct in the future then the same way would a priori prevent from protecting all systems oxaliplatin/impurities containing the very same quantity of oxalic acid but having considerably less contents of the other accompanying impurities when comparing the latter with those reachable to priority date of D1. In our estimation, this would be against the fair practice since these systems will be both novel (having different content of at least one

accompanying impurity over the prior art systems) and inventive (having a better quality owing to a reduced content of the accompanying impurities in comparison with the prior art systems) and should be thus allowed to be protected.

By the way, we are prepared to prove in the following that the oxaliplatin system according to claim 1 of the present application is matter-of-factly different as to its composition from the oxaliplatin system of D1. The thing is, the process according to claim 3 of D1 for preparing the oxaliplatin system according to claim 1 of D1 optionally uses potassium iodide or sodium iodide in the step (c) and obligatorily uses an alkali metal salt of oxalic acid in the step (d) which means these two steps considerably load the process system with the alkali metals that hardly can be perfectly washed off during the final washing of oxaliplatin with water taking into account that said washing can not be extensive since otherwise an undesired dissolution rate of oxaliplatin and thus also a non-neglectable loss thereof would all the same occur. Contrary to the process of D1, the process of the present application uses quaternary ammonium iodide and oxalic acid instead of potassium iodide/sodium iodide and an alkali metal salt of oxalic acid, respectively, as a result of which no alkali metals are in this case introduced into the process system which , in turn, enables the resulting oxaliplatin to have an excellent content of the alkali metals not exceeding 0,01%. It is obvious from the foregoing that such an extreme low content of the alkali metals can be by no means reached when oxaliplatin should be prepared in an acceptable yield following the process of D1. The oxaliplatin system of the present application should be thus justifiably considered to be novel against that of D1 since it at least contains, taking account of the above displayed facts, a different amount of the alkali metals when this is compared with that of the oxaliplatin system of D1.

Item 3a) To the allegation of the ISA stipulating that "*as the subject of claim 1 is considered not to be novel,*

it is also considered to be not inventive (Article 33(3) PCT)": As the non-novelty objection of the subject-matter of claim 1 of the present application has been refuted on base of the above-gathered arguments this non-novelty should have no negative impact upon the inventiveness of said subject-matter any more. The inventiveness of the oxaliplatin system of the present application in fact consists in that this system affords better product having, in comparison with the relevant prior art, reduced content of the accompanying impurities which is highly desired when this product is to be used in the field of pharmaceutical compositions. The fact should not be neglected that also the process of the present application is able to provide the content of oxalic acid being not more than 0,08 % as claimed for the oxaliplatin system of D1. The thing is that example of the present application quotes for the oxaliplatin system of the present application a content of oxalic acid lower than 0,01 % by weight (also in this case, only the detection limit of the used analytical method is the case) which also is under the detection limit of 0,02 w/w % for oxalic acid mentioned in example 1 of D1 and even yet better.

Item 3b) The ISA is of the opinion that "*an unexpected effect* supporting the inventiveness of the subject-matter of process claims 2,3 of the present application *could be e.g. a more efficient process or an improved product*". As already discussed in the item 2b, the oxaliplatin system of the present application is really an improved product over that of D1 since it has a comparable or even better content of oxalic acid and better content of at least one accompanying impurity (alkali metals). According to above ISA´s stipulation, already this reality alone should evidence in favor of the presence of the inventive step in the process of the present application. Nevertheless, the process of the present application is a more efficient process over that of D1, as well. The prior art process of D1 is described in the second paragraph of page 3 of the present application according to which the substantial drawback of this prior art process is that "*although*

oxaliplatin is only slightly soluble in water at room temperature, it is obvious from example 1 of said international patent application that washing with water causes losses of about 20 % of oxaliplatin in one single operation only, i.e. during recrystallisation". Unlike this, the process of the present application is not burdened with such high losses. The thing is, the absence of the alkali metals in process system caused by the use of quaternary ammonium iodide and oxalic acid instead of potassium iodide/sodium iodide and alkali metal salt of oxalic acid, respectively, enables to also use as washing medium polar organic solvents, such as ethanol in which all the concerned undesired impurity of oxaliplatin are better soluble than in water as opposed to oxaliplatin that is on the contrary less soluble therein. In addition, the acidity of the process medium induced by the use of oxalic acid favorably influences the stability of oxaliplatin and thus the global yield thereof.

Taking into account the foregoing, the matter as claimed in claims 1 to 3 of the present application is, to our mind, not only novel but also includes the inventive step.

In behalf of the Applicant

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